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09/449,077	11/24/1999	Dr. Thomas Hunig	12254/	5838

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PAUL C REMUS
DEVINE MILLIMET & BRANCH PA
111 AMHERST STREET
PO BOX 719
MANCHESTER, NH 03105

EXAMINER	
ROARK, JESSICA H	
ART UNIT	PAPER NUMBER
1644	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/449,077	Applicant(s) HUNIG, DR. THOMAS	
	Examiner Jessica H. Roark	Art Unit 1644	

-- Th MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 1999 and 30 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *5-12,16-23 and 25-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13-15 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 11/24/99, 11/24/99 and 8/30/01 (Paper Nos. 4, 5 and 11), are acknowledged.

Claims 13-40 have been added.
Claims 3-5, 7 and 11-12 have been amended.
Claims 1-40 *are pending.*

2. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground that an undue searching burden has not been established. This is not found persuasive because as set forth in Paper No. 9, the different Groups are distinct and have acquired a separate status in the art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-12, 16-23 and 25-40 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-4, 13-15 and 24 *are under consideration in the instant application.*

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on May 28, 1997. It is noted, however, that applicant has not filed a certified copy of the 197 22 88.7 application as required by 35 U.S.C. 119(b).

Until such time as a certified copy of the foreign priority document is filed, the instant claims are considered to have a priority date of May 28, 1998, the date of filing of parent application PCT/DE98/01499.

4. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

5. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(d) Brief Summary of the Invention.
(e) Brief Description of the Several Views of the Drawing(s).
(f) Detailed Description of the Invention.
(g) Claim or Claims (commencing on a separate sheet).
(h) Abstract of the Disclosure (commencing on a separate sheet).
(i) Drawings.

Applicant is requested to minimally provide the appropriate headers for the various sections found in the instant specification.

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the in the specification.

7. Claims 2-4, 13-15 and 24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claim 1 recites a "human-compatible monoclonal antibody", whereas the dependent claims only recite the broader class of "monoclonal antibodies".

8. Claims 13-15 and 24 are objected to because of the following informalities: in section (a), it appears that the last phrase should read -- *which* carry the plasmid – rather than "*with* carry the plasmid". Appropriate correction is required.

9. Claim 13 is objected to because of the following informalities: in section (h), it appears that the last phrase should read -- obtained in *phase* g) -- rather than "obtained in *phage* g".

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

11. Claims 1-4, 13-15 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-4, 13-15 and 24 are ambiguous in that it is unclear if a compound or composition is claimed. Because the preamble recites "antibodies" or "hybridoma cells" in the plural, this indicates a mixture of components. However, it appears that compound claims are intended. It is suggested that Applicant amend the claims to recite the singular forms -- antibody-- and -- hybridoma cell --.

B) Claims 2-4, 13-15 and 24 recite the limitation "monoclonal antibodies" in the preamble. There is insufficient antecedent basis for this limitation in these claims. Independent claim 1, from which all other claims depend either directly or indirectly, recites a particular type of monoclonal antibody, a "human-compatible monoclonal antibodies". Thus the dependent claims do not further limit the independent claim, leading to confusion as to the metes and bounds of the dependent claims.

Applicant should amend the claims so that the preambles are consistent.

C) Regarding claims 2, 13-14 and 24, the phrase "if applicable" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

D) Regarding claims 2, 13-14 and 24, the phrase "for example" renders the claims indefinite because it is unclear whether the limitation following the phrase is part of the claimed invention. See MPEP § 2173.05(d).

E) Claims 2-3 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step in each case is the resolution step: for example, "isolating the monoclonal antibody produced by the hybridoma cells".

F) Claims 3-4, 13-15 and 24 are indefinite in the recitation of the phrase "in this way" because it is unclear what steps are encompassed by this phrase. Applicant should amend the claims to either recite steps, or if the intent is to refer to the preceding step, the phrase should be amended to indicate that step by reference to the letter (e.g., as in step "c" of the instant claims).

G) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-4, 13-15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over June et al. (US Pat No. 5,858,358) in view of Tacke et al. (Eur. J. Immunol. January 1997; 27:239-247), and in further view of Applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864).

The claims are drawn to human-compatible monoclonal antibodies to human CD28 which activate human T lymphocytes without occupancy of an antigen receptor, and to hybridomas producing such antibodies.

June et al. teach antibodies to human CD28, and the production of hybridomas producing anti-human CD28 antibodies (see entire document, especially columns 5-6 and 12-17). June et al. teach that cells transfected with human CD28 can be used to immunize mice and the hybridomas producing anti-human CD28 antibodies isolated (e.g., columns 12-17). June et al. also teach that antibodies which stimulate T cell proliferation are highly desirable because they can be used to expand T cells for treatment of individuals with low numbers of T cells, as occurs in HIV infection, as well as to expand T cells for therapies requiring stimulation of an immune response (see especially columns 18-20).

June et al. do not teach humanized antibodies or test whether any of the antibodies to human CD28 are able to directly stimulate T cells.

Tacke et al. teach the production of hybridomas secreting a rat antibody to human CD28 and the characterization of the rat antibody JJ316 (see entire reference, e.g., Abstract). Tacke et al. teach that the rat antibody JJ316 is specific for rat CD28 and can activate proliferation of all T cell subsets without T cell receptor occupancy (see entire document, especially Figure 2 and section 3.4). Tacke et al. also teach that the ability of the JJ316 antibody to "directly" stimulate is due to a difference in fine specificity versus other anti-CD28 antibodies that do not directly stimulate; and that antibodies with this fine specificity can be generated by immunizing with CD28 transfected cell lines more readily than by immunizing with T cells which naturally express CD28 (see especially page 245, 2nd column).

Tacke et al. do not teach hybridomas producing antibodies to human CD28 or humanization of anti-CD28 antibodies.

However, given the teachings of Tacke et al. that directly stimulating antibodies can be produced by immunizing with a cell line transfected with human CD28, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies taught by June et al. (or to produce additional antibodies) for those monoclonal antibodies and the hybridomas producing them which are specific for human CD28 and which directly activate human T cells without occupancy of the T cell antigen receptor. One would have been motivated to screen for such antibodies and hybridomas producing them in order to derive antibodies that could be used without anti-CD3 antibodies in the methods of June et al. to expand T cells for human therapy. Given the teachings of Tacke et al. that anti-CD28 antibodies which directly stimulate T cells without occupancy of the T cell receptor are produced using immunization strategies based upon transfected cell lines rather than T cells, and the teachings of June et al. that transfected cell lines could be and were used; one of ordinary skill in the art would have had a reasonable expectation that directly stimulating antibodies specific for human CD28 were produced or could be produces using the method of June et al. and could be identified as taught by Tacke et al.

Neither Tacke et al. nor June et al. teach humanization of the antibodies to human CD28.

However, as acknowledged by Applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).

It would have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by June et al., including those antibodies which directly activate T cells without occupancy of the T cell antigen receptor. Given the art-recognized methods of humanizing antibodies, as acknowledged by Applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

With regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1-4, 13-15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siefken et al. (Cell. Immunol. February 1997; 176:59-65), in view of Applicant's acknowledgement on page 4 of the specification at lines 1-8 that production of hybridoma cells, humanization of antibodies, and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidenced by Bendig et al. (US Pat No. 5,558,864).

The claims are drawn to human-compatible monoclonal antibodies to human CD28 which activate human T lymphocytes without occupancy of an antigen receptor, and to hybridomas producing such antibodies.

Siefken et al. teach the production of hybridoma-produced antibodies to human CD28 and that the BW 828 antibody could activate human T cells without co-engagement of the T cell antigen receptor/CD3 complex (see entire document, especially "Materials and Methods" and "Discussion").

Siefken et al. do not teach humanization of anti-CD28 antibodies.

However, as acknowledged by Applicant on page 4 at lines 1-8, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, especially columns 21-22).

It would therefore have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by Siefken et al. Given the art-recognized methods of humanizing antibodies, as acknowledged by Applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach that the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

With regards to the various method steps recited in the production of the monoclonal antibodies and hybridomas, it is noted that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
November 15, 2001

PHILLIP GAMBEL, PH
PRIMARY EXAMINER
TECH CENTER 1600
11/15/01